Costa Rica, 58% (n = 674); Cuba, 6% (n = 80); Ecuador, 25% (n = 1363); Guatemala, 64% (n = 1483); Honduras, 12% (n = 393); Mexico, 52% (n = 497); Nicaragua, 20% (n = 296); Paraguay, 44% (n = 980); Peru, 80% (n = 1407); Uruguay, 59% (n = 1431) and Venezuela, 25% (n = 2114).

Similarly, data submitted to the Pan-American Association of Infectious Diseases for the year 2006 showed the following rates of HA-MRSA: Argentina 51%; Bolivia 55%; Brazil 54%; Chile 29%; Ecuador 25%; Mexico 32%; Panama 28%; Paraguay 30%; Uruguay 24%; and Venezuela 27% The first published report of CA-MRSA infections in Latin America came from Brazil, where three wellcharacterized strains, isolated from patients with SSTIs or septic arthritis in 2003, harbored SCCmec type IV, PVL, enterotoxin and #-hemolysin genes. A further report followed of a large outbreak of CA-MRSA infection that affected inmates in jails and people from the community in Montevideo, Uruguay, beginning in January 2002. At the end of the outbreak, more than 1000 patients had been affected and 12 deaths had occurred. SSTIs accounted for more than 65% of the cases, but severe forms of pneumonia were reported, including 4 deaths. In this outbreak, TMP-SMX was very active in the treatment of skin infections.

Since those first reports, MRSA has been identified as the cause of community-acquired infections in several more countries across South America. In Lima, 27% resistance to methicillin was reported in isolates collected from 30 community-acquired infections in 2002. Two cases of SSTI caused by CA-MRSA strains were reported from Bogotá in 2006, and a report from the Colombian network of resistance surveillance showed an increase in CA-MRSA from 1% of S. aureus isolates in 2001 to 5.4% in 2006 [21]. The PAHO program has also included surveillance of community-acquired MRSA infections since 2005, and in Venezuela, 12.4% of 845 isolates of S. aureus from the community were resistant to oxacillin. However, no clinical information is available for these cases. A few isolated cases of CA-MRSA infection have been reported in Chile, but some of these were in people returning from cities in Uruguay or Brazil with a high incidence of MRSA.

MRSA is an increasing problem in Latin America, both in the healthcare environment and in the community. In nosocomial *S. aureus* infections, the frequency of methicillin resistance has surpassed 50% in over half of the Latin American countries for which data were identified. Community-acquired-MRSA has been reported in Latin America and even though large outbreaks such as the one that occurred in Uruguay — causing 12 deaths — have not been reported elsewhere, this example highlights the problem. Surveillance programs are only recently beginning to record CA-MRSA, and the true incidence of MRSA in the community is still largely unknown in the region.

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67.001

Microbial chemical ecology and the future of antibiotics

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When it comes to cell-to-cell communication the predominant language is that of small signaling molecules. The microbial world is no exception - microbes are known to exchange messages both within and across species by secreting and recognizing small molecule natural products. Among such compounds can be found many of the antibiotics that have been extensively used in medicine since the middle of the last century. Concomitant with their use has been the evolution of antibiotic resistance. In order to understand the phenomenon of antibiotic resistance and to devise better strategies for future antibiotic discovery and use it is useful to consider this topic from an ecological perspective. In this sense, it is important that to recognize that we remain largely ignorant of the role that antibiotic substances play in environmental settings. Work that I will discuss in this lecture supports the idea that antibiotics can serve non-lethal signaling functions in bacteria - both within and across species. In addition, I will discuss instances in which interspecies interactions mediated by small molecule natural products lead to narrow spectrum action of antibiotics in ecological settings. These results suggest new ways to look for and use antibiotics in the future.

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Tuberculosis: Tools for the Future (Invited Presentation)

68.001

Unlocking the Mycobacterial Cell Wall: Insights into Virulence, Biosynthetic Pathways and systems-based approach to drug discovery

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Biosynthetic machinery of complex lipids in *Mycobacterium tuberculosis* (Mtb) includes a family of FadD proteins, which are otherwise universally involved in fatty acid degradation. Mtb produce several exotic lipids, many of which are important for its virulence as well as survival in the host. By combination of structural, genetic and biochemical studies, we have identified several novel mechanisms and pathways that generates complex cell envelope lipids. We show that polyketide synthase in conjunction with a new family of fatty acyl AMP ligases (FAALs) in Mtb are involved in biosynthesis of lipids. Based on the structure of a FAAL homologue and by generating loss- as well as gain-of-function mutants, we show that an insertion motif dictates the synthesis of acyl-adenylates or acyl-CoA, and thus bifurcates metabolic fate of fatty acids. Since FAALs

are focal nodes in biosynthetic network of virulent lipids, inhibitors directed against these proteins provide a unique multi-pronged approach of simultaneously disrupting several pathways in lipid metabolism. Our study illustrate how obligate pathogens like Mtb have evolved such novel themes of functional versatility to generate unusual metabolites. We also reveal possible evolutionary path traced by FAALs from omnipresent fatty acyl CoA ligases. Furthermore, our study also provide credence to the 'systems pharmacology' approach for drug discovery.

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68.002

Diagnosing Drug Resistance in Low-Resource Settings: Practical Approaches

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Tuberculosis (TB) remains one of the major causes of death from a single infectious agent worldwide. Of great concern for TB control is the emergence of drug resistance. Since there is no cure for some multidrug-resistant strains of *Mycobacterium tuberculosis*, there is concern that they may spread around the world, stressing the need for additional control measures, such as new diagnostics, better drugs for treatment, and a more effective vaccine. Pulmonary TB can be diagnosed by its symptoms, chest radiography, sputum smear microscopy and by cultivation of *M. tuberculosis*, which is considered as the gold standard. Recent advances in molecular biology and molecular epidemiology, and a better understanding of the molecular basis of drug resistance in TB, have provided new tools for rapid diagnosis; however, the high cost of most of these techniques, and their requirement for sophisticated equipment and skilled personnel have precluded their implementation on a routine basis, especially in low-income countries. Other nonconventional diagnostic approaches proposed include the search for biochemical markers, detection of immunological response and early detection of *M. tuberculosis* by methods other than colony counting. In the present mini review, some of these approaches will be reviewed and the feasibility for their implementation in diagnostic laboratories will be discussed. However, with the resurgence of interest in the development of new tools for TB control, and the recent influx of funding and political support, it is likely that the next few years will see the introduction of new diagnostic tools into routine TB control programs and particularly in high disease burden, and resource-poor countries.

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68.003

Applicable Insights from Pharmacokinetic and Pharmacodynamic Modeling of Antituberculosis Chemotherapy

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Current chemotherapy for tuberculosis leaves considerable room for improvement. Major objectives include shortening the duration of therapy necessary for cure, improving the efficacy of intermittent treatment regimens, and preventing the development of drug resistance. Better understanding of the pharmacodynamic relationship between drug exposure and drug effect will identify strategies for optimizing drug effect in order to achieve these objectives, thereby informing pre-clinical drug development, clinical trial design and clinical practice. Recent work in *in vitro* and animal models involving both new and existing antituberculosis drugs will be reviewed and discussed in this context.

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68.004

Addressing Latent TB in Areas with High TB Burden: Implications for Control

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Brazil is a country in South America with a total population of 191 million of people (81% urban; 19% rural) with an estimated incidence of 92,000 new cases of tuberculosis (TB) yearly (data from 2007). Treatment of latent TB infection (LTBI) in Brazil is currently recommended only in the case of contacts of pulmonary smear-positive TB patients aged % 15 years with a tuberculin skin test (TST) ''10 mm and no previous bacilli Calmette-Guérin (BCG) vaccination or with a TST'' 15 mm regardless of previous BCG vaccination. However, a recent retrospective cohort study evaluating contacts aged ''15 years who did not meet the Brazilian criteria for LTBI treatment shown a TB incidence of 3.2% (22/667), with an estimated TB rate of 1,649 per 100 000 population. The risk of TB was greater among the 349 contacts with TST'' 5 mm (5.4%) compared to the 318 contacts with TST < 5 mm (0.9%; RR 6.04, 95%CI 1.7—20.6). The high incidence of TB among contacts who did not meet the Brazilian criteria for LTBI treatment strongly suggests that a change on these criteria could have a direct impact on TB control.

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